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Radiotherapy to Control CNS Lymphomatoid Granulomatosis: A Case Report and Review of the Literature

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Lymphomatoid granulomatosis (LG) is an uncommon but potentially fatal disease. The disease primarily involves the lungs; however, skin, renal, and central nervous system (CNS) are seen in varying proportions. Neurological involvement occurs in one third of the patients, and confers a worse prognosis. The use of radiotherapy to treat CNS involvement in LG has not been well studied. We report a case of a 33-year-old man with multiple CNS lesions treated successfully with radiotherapy and review 6 other cases in the literature using similar treatment. These cases support the use of radiotherapy for CNS involvement in LG. Am. J. Hematol. 62:239–241, 1999. © 1999 Wiley-Liss, Inc.

Key words: lymphomatoid granulomatosis; central nervous system; radiotherapy; case report

INTRODUCTION

Lymphomatoid granulomatosis (LG) is an uncommon and unusual multisystem disease that has characteristics of an inflammatory granulomatous process as well as those of a lymphoproliferative disease. Histologically it is characterized by a polymorphic infiltrate of atypical lymphoid and plasmacytoid cells with granulomatous inflammation in an angiocentric and angiodestructive pattern [1]. Neurological manifestations occur in 30% of the patients and are the presenting complaint in 21% [1,2]. The prognosis of LG is extremely poor, with a mortality of 65–90%, worsened by neurological involvement [2].

Approximately 200 cases of LG have been reported in the literature [1–4]. The majority were treated with chemotherapy and steroids. Radiotherapy has been used to treat LG skin lesions [5,6]. The use of radiation treatment for CNS LG is less well described, with only 6 cases reported.

We describe the case of a 33-year-old man with LG of lungs and brain, successfully treated with radiation therapy.

CASE REPORT

A 33-year-old Caucasian male presented in May 1993 with fever, rigors, and anorexia. Laboratory investigation demonstrated a transient hepatitis, but a persistent pancytopenia with a white count of 2.0, platelets of 80, and hemoglobin of 113. Bone marrow aspirate and biopsy were normal. A CT scan and ultrasound of the abdomen showed splenomegaly. His chest X-ray showed diffuse interstitial infiltrates, with negative tuberculin skin test, serology, and blood cultures. He was discharged from hospital in June with a diagnosis of pyrexia of unknown origin.

He was readmitted in July 1993 with fever, cough, and a 30-pound weight loss but no neurologic symptoms. Chest X-ray and CT revealed worsening bilateral diffuse reticular pattern with small peripheral nodules. Ultrasound and CT scan of abdomen still showed splenomegaly. CT scan of head was normal. Laboratory values revealed a white blood cell count of 2.6×10^9/l, hemoglobin 117 g/l, platelets 121×10^9/l, ESR 16, with negative rheumatoid factor and ANA. His CD4-CD8 ratio was 2.7 with an absolute CD4 count of 0.39. Bone marrow aspirate and biopsy were nondiagnostic. Tissue from

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TABLE I. Cases of Lymphomatoid Granulomatosis with CNS Involvement Treated with Radiotherapy

Authors	Age/gender	System	Therapy	Outcome
Simon et al. [11]	64-yr male	- -Nasopharyngeal -CNS	-Cyclophosphamide -Prednisone -Whole brain irradiation	-Improvement in neurological status -Died 1 year after onset of symptoms from complications of biopsy site
Kerr et al. [14]	36-yr female	CNS	-Partial temporal lobectomy -Radiotherapy	-Symptom free 8 months post radiotherapy
Shank et al. [13]	56-yr female	-Skin -CNS	-Left parietal craniotomy -Cyclophosphamide and prednisone post surgery -Whole brain irradiation	-Neurological improvement -Doing well 16 months post irradiation
Simard et al. [10]	40-yr female	-Lung -CNS	-Cyclophosphamide -Prednisone -Radiotherapy	-Neurological improvement -Doing well 18 months post radiotherapy
Hamilton et al. [9]	60-yr male	CNS	-Posterior fossa craniectomy -Radiotherapy post surgery -Dexamethasone	-No residual tumor 2 months post radiotherapy -New lesion at 16 months -Further surgery and radiotherapy -Died 41 days post surgery -Meningitis and empyema
Kleinschmidt-DeMasters et al. [12]	60-yr male	CNS	-Prednisone -Whole brain irradiation	-Marked improvement 4 years post treatment

an open lung biopsy revealed an angiocentric and angiodestructive infiltrate of atypical T lymphocytes, of lymphomatoid granulomatosis. Six cycles of CHOP chemotherapy were given from July to November with complete resolution of the lung lesions and splenomegaly.

In December 1993, on tapering doses of prednisone, he developed ataxia, vertigo, diplopia, left facial numbness, and dysarthria. A week later he experienced sudden loss of vision in his left eye with a Marcus–Gunn pupil on the left and loss of the left nasal field. A MRI showed three lesions in the left brain stem in the lateral superior pons, in the middle cerebral peduncle and in the right parietal lobe, compatible with stroke or lymphomatous involvement. A 2D echo and a transesophageal echo were normal. Despite therapeutic anticoagulation he continued to have further neurologic symptoms. In January 1994, he experienced transient left arm and leg weakness, which recurred 3 weeks later. Repeat MRI showed lesions in the posterior and both carotid circulations, with no evidence of meningeal irritation or vasculitis. A cerebral angiogram was not diagnostic. In February, he developed sudden onset dysarthria, right facial weakness, and dysdiadochokinesis. The cumulative effect of these neurological events had left him bed-ridden and unable to feed himself. He was referred to the Hamilton Regional Cancer Clinic for assessment of radiation therapy.

He received 40.00 Gy in 20 fractions of cobalt X-rays to his whole brain over 28 days while remaining on prednisone. Field borders inferiorly were at 0.5 cm below the supraorbital ridge and 1 cm below the pinna, to ensure temporal lobe and brain stem coverage. The other 3 borders were in air. Improvement in clinical symptoms and signs was seen after 2 weeks of radiation treatment, with significant improvement in dysarthria, balance, and vision. The prednisone was tapered over 6 months with no further recurrence of symptoms. Repeat CT scan of his chest and abdomen showed no evidence of disease. Over the ensuing months his speech, strength, and vision returned to normal. He was left with mild balance impairment, which resolved slowly over the next 3 years; by December 1997 he was able to resume ice skating. He remains in complete clinical remission as of February 1999.

DISCUSSION

Our patient presented with LG in the lungs and spleen with later development of cerebral and cranial nerve involvement *after* therapy induced remission of the visceral disease. In 1979, Katzenstein et al. [2], reported that 30% of their 152 patients had neurological disease with 19% having CNS signs, 11% cranial nerve palsies, and 7% peripheral neuropathies. The neuropathologic findings are diverse, with direct infiltration of nerves by atypical lymphoid cells, vascular thrombosis, and infarction as a result of vasculitis, intracerebral granuloma formation, and diffuse pleomorphic infiltration of the meninges, blood vessels, and brain [1].

Six cases of successful radiotherapy in cerebral LG have been previously reported (see Table I). In 3 of the 6 cases, the cerebral lesions had been resected prior to the radiotherapy. All 6 cases showed neurological improvement post radiation, with radiological improvement in 3 cases [9–11]. Two of the 6 patients died from complications of the biopsy or their surgery, not from their disease. The other 4 patients had stable neurological status at 8 and 16 months [9,13], and 10 and 13 years post radiation therapy (P. Leblanc and C. M. Filley, personal communication). Our patient remains symptom free 5 years post radiation treatment and 6 years since diagno-

sis. In previous reviews, CNS involvement was reported as a grave prognostic sign associated with a mortality of 86% at 14 months compared to 66% for those without CNS involvement [2].

In the cases presented in Table I, the total radiation dose varied from 30.00 to 45.00 Gy. Given the small number it would be difficult to draw any conclusion about the most effective dose. Our patient received a total of 40.00 Gy in 20 fractions, with a low dose of 2.00 Gy per fraction to reduce risks of long term cognitive deficits. The total dose of 40.00 Gy was selected because lymphocytes in the brain may be more radioresistant than lymphocytes in nodal or cutaneous microenvironments. Our patient received prednisone during his radiotherapy, as did five of the six cases reviewed [9–13]. Three of the six cases were treated also with cyclophosphamide for nasopharyngeal, skin, and lung involvement. Although cyclophosphamide successfully reversed the lung disease the persistent CNS involvement is likely related to poor penetration of the blood–brain barrier. Given the high morality of LG with CNS involvement, the data reviewed here suggest early consideration of the use of radiotherapy in treating CNS involvement.

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